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ORIGINAL PAPER

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Efficacy and safety of intravenous amiodarone for incessant tachycardias in infants

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Abstract Amiodarone is an effective anti-arrhythmic agent for the treatment of supraventricular and ventricular tachycardias. The safety and efficacy of intravenous amiodarone has been described in adults and children but only to a limited extent in infants. The purpose of this study was to evaluate the safety and efficacy of intravenous amiodarone in infants. Between February 1994 and June 2001, 23 infants with a median age of 8 days (range 1–300 days) with life-threatening incessant tachycardias (17 supraventricular, 6 ventricular) were treated with intravenous amiodarone as single anti-arrhythmic agent. At presentation, 22 infants were haemodynamically unstable. Amiodarone was given as an intravenous loading dose of 5 mg/kg over 1 h followed by an intravenous maintenance dose of 5 μg/kg per min with stepwise increase up to 25 μg/kg per min until arrhythmia control or side-effects occurred. Amiodarone was effective in 19 infants, partially effective in three and ineffective in one infant. The median time until arrhythmia control was 24 h (range 1–96 h) and the median maintenance dosage 15 μg/kg per min (range 5–26 μg/kg per min). Electrophysiological side-effects necessitating dose reduction comprised of sinus bradycardia in two patients. Hypotension in one patient resolved after dose diminution. Neurological side-effects consisted of choreatic movements in one infant, which resolved over time. Amiodarone administration was stopped in one patient with elevated liver enzymes. *Conclusion*: Intravenous amiodarone is a safe and effective therapy for life-threatening incessant tachycardias in infants.

Keywords Amiodarone · Infants · Tachycardias

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Introduction

Amiodarone has been found to be effective in the treatment of supraventricular and ventricular tachycardias in adult and paediatric patients [2, 8,9]. Various studies have demonstrated the superior anti-arrhythmic effect of amiodarone compared to other anti-arrhythmic agents [2, 3, 8,9]. Moreover, unlike other anti-arrhythmic drugs, amiodarone has a low negative inotropic effect and can be safely used in patients with decreased contractility and end-stage heart failure [1, 3, 4, 6, 7,10]. Amiodarone-related side-effects are less pronounced in paediatric patients than in adults [1,6]. Because of its anti-arrhythmic efficacy and low negative inotropic effect, intravenous amiodarone has been used in children with life-threatening supraventricular or ventricular tachycardias [3, 4,7]. Thus, intravenous amiodarone may be the preferred anti-arrhythmic treatment for infants and children with depressed myocardial function due to incessant tachycardias or tachycardias arising in the perioperative period of surgery for congenital heart disease. Besides the potentially faster anti-arrhythmic effect, intravenous drug administration may also be prompted by the inability of an oral route in infants and children with severe heart failure or after previous cardiac surgery [2]. However, there are concerns about the safety of intravenous amiodarone, which also contains chemicals with negative inotropic and hypotensive effects in the solution [2, 5,11]. Moreover, there is a possibly more negative inotropic effect of amiodarone on the developing myocardium due to calcium channel blocking activity [2]. Previous studies have also shown that acute effects of amiodarone on the electrophysiological properties are different in the neonatal and adult cardiac fibre [13].

Reports about the administration of intravenous amiodarone in infants are scarce. The aim of the present study was to determine the safety and efficacy of intravenous amiodarone in infants for the treatment of incessant tachycardias.

Subjects and methods

Subjects

This study is a retrospective analysis of data from 23 infants (15 males, 8 females) who were treated from February 1994 to June 2001, with intravenous amiodarone. Characteristics of the group are listed in Table 1. The majority of patients was in respiratory distress and showed haemodynamic instability requiring ventilation and cardiovascular support. Only one patient who was followed for ventricular premature beats in the neonatal period was asymptomatic and presented with incessant monomorphic ventricular tachycardia. Compliant with other published recommendations, intravenous amiodarone was used as single anti-arrhythmic agent for infants with incessant monomorphic and polymorphic ventricular tachycardias, incessant supraventricular tachycardias with an ejection fraction $<45\%$ or infants in the post-operative period after congenital heart surgery with compromised haemodynamics necessitating cardiopulmonary support [3, 4, 7,9]. Treated arrhythmias were supraventricular tachycardias in 17 and ventricular tachycardias in 6 infants (Table 2). All arrhythmias were diagnosed by standard 12-lead ECG or ECG derived from the intensive care unit monitoring system with the addition of oesophageal or temporary pacing wire ECG in case standard ECGs were not conclusive. Intravenous amiodarone was administered under continuous intensive care unit ECG monitoring and daily 12-lead ECG recordings to confirm arrhythmia control and to exclude pro-arrhythmic drug side-effects and QTc prolongation. After replacement of intravenous amiodarone by oral amiodarone, patients were followed at 3 months intervals with 12-lead ECG, 24 h Holter monitoring, liver and thyroid function tests.

Fetal arrhythmias were observed in four patients but were not treated before birth. Only one patient with an atrioventricular re-entrant tachycardia had previously received a class 1c anti-arrhythmic agent that did not control the arrhythmia but worsened the haemodynamic situation. Adenosine was administered in patients with atrioventricular re-entrant tachycardias but sporadic tachycardia terminations were always followed by near immediate tachycardia re-initiations. Two infants with atrial fibrillation and intra-atrial re-entrant tachycardia respectively were treated with intravenous amiodarone after D/C cardioversion or overdrive pacing failed. However, in three infants with observed on/off phenomenon of intra-atrial re-entrant tachycardias, intravenous amiodarone was administered as first line therapy.

Table 1 Characteristics of the study group of 23 infants. Variables are number of patients or median and range

Variable	
Age (days)	8 (1–300)
Weight (kg)	3.5 (2.4–8.2)
Follow-up (months)	18 (1–72)
Intrauterine tachycardias	4
Cardiac anatomy	
Structurally normal heart	10
Congenital heart disease	10
Cardiomyopathy	3
Cardiac surgery	8
Symptoms	
Respiratory distress	10
Post-operative haemodynamic instability	8
Cyanosis	2
Syncope/resuscitation	2
No symptoms	1

Drug administration protocol

Published protocols for intravenous amiodarone in paediatric patients were adjusted concerning the maximum maintenance dosage based on reports indicating the need for higher oral dosages in children compared to adults [1, 3, 4, 7, 8,14]. After an intravenous amiodarone loading dose of 5 mg/kg over 1 h, an initial intravenous maintenance dose of 5 μg/kg per min was increased every 6 h in 2.5 μg/kg per min steps up to 25 μg/kg per min until the arrhythmia was controlled or pro-arrhythmic or haemodynamic side-effects occurred. Intravenous amiodarone was replaced by oral amiodarone when oral feeding was tolerated in infants with controlled arrhythmias. To avoid the risk of arrhythmia recurrences, no attempts were made in patients with amiodarone controlled arrhythmias to switch to other anti-arrhythmic agents at the time of change to oral amiodarone. A drug loading phase of approximately 10 mg/kg amiodarone daily for 10 days was intended for intravenous as well as combined intravenous and oral administration. Oral amiodarone therapy was then continued for about 1 year.

Definition of drug efficacy, pro-arrhythmia and side-effects

As described previously, anti-arrhythmic therapy was considered effective if regular sinus rhythm was restored and the clinical status improved, partially effective if the arrhythmia persisted but the ventricular rate slowed and symptoms improved and ineffective if arrhythmias and symptoms persisted [4]. Time to arrhythmia control was defined as time from intravenous loading dose to sinus rhythm without any tachycardia episodes. The

Table 2 Characteristics of arrhythmias and amiodarone therapy in 23 children. Variables are number of patients or median and range. (*AET* atrial ectopic tachycardia, *AFib* atrial fibrillation, *AVRT* atrioventricular re-entrant tachycardia, *IART* intra-atrial re-entrant tachycardia, *VT mon* monomorphic ventricular tachycardia, *VT poly* polymorphic ventricular tachycardia)

Arrhythmias	*N*	Patients after previous cardiac surgery	Heart rate pre therapy (bpm)	Heart rate on therapy (bpm)	Therapy effective[a]	Time to effect (h)	Maximum iv amiodarone dose (μg/kg per min)	Days of iv amiodarone
AVRT	8	2	248 (212–269)	135 (100–155)	7	39 (7–96)	15 (5–20)	5 (1–12)
AET	4	1	194 (157–227)	123 (111–131)	3 (1)	24 (3–63)	13.8 (7–16)	11 (4–14)
IART	4	3	182 (150–283)	129 (115–144)	4	7.5 (1–24)	10 (8–15)	3.5 (1–6)
AFib	1	0	300	152	(1)	24	5.0	3.0
VT mon	4	2	208 (165–211)	137 (132–154)	4	21.5 (8–40)	15 (5–15)	7.8 (3–24)
VT poly	2	0	284 (198–370)	150 (149–151)	1 (1)	1	15.5 (5–26)	8.5 (3–14)
All patients	23	8	224 (150–370)	134 (100–155)	19 (3)	24 (1–96)	15 (5–26)	5 (1–24)

[a]In brackets number with partial effect

evaluation of pro-arrhythmic effects was based on previous definitions but included also a QTc prolongation ≥ 500 ms in the absence of pre-excitation, bundle branch block or intraventricular block [12]. Neurological, liver or thyroid dysfunction and haemodynamic effects necessitating amiodarone dosage reduction or cessation of drug administration were considered as significant side-effects. Ophthalmological follow-up was not performed in infants as the examination had to be done under general anaesthesia which was considered to be inadequate for a 1-year treatment period.

Statistics

Data were analysed by using descriptive statistics and expressed as median and range. A non-paired student t-test was used where applicable. A P value of < 0.05 was considered statistically significant.

Results

Arrhythmia control

Details of arrhythmias and amiodarone therapy are described in Table 2. Intravenous amiodarone was given to 23 infants, 17 with incessant supraventricular tachycardias and ejection fraction $< 45\%$ or haemodynamic instability (eight post-operative) and six for incessant ventricular tachycardias. Intravenous amiodarone was effective or partially effective in 22 of 23 patients. Partial effects in three infants consisted of tachycardia rate slowing in a polymorphic ventricular tachycardia and an atrial ectopic tachycardia, and ongoing non-sustained runs of atrial tachycardia in an infant with cardiomyopathy and atrial fibrillation respectively. The partial effect of slowing the tachycardia rate in two infants allowed to stabilise them haemodynamically and then to control the arrhythmia with a combination therapy adding oral propafenone to oral amiodarone. No effect was achieved in an infant with atrioventricular re-entrant tachycardia.

In 12 patients with marked haemodynamic instability, anti-arrhythmic therapy was possibly jeopardised by the concomitant administration of vasoactive substances or inotropes. However, the concomitant use of these potentially pro-arrhythmic agents did not influence efficacy, time to arrhythmia control or required amiodarone dosages (amiodarone maintenance dosage 12.2 ± 4.6 μg/kg per min without inotropes versus 12.1 ± 6.1 μg/kg per min with inotropes, $P = 0.95$).

Although intravenous amiodarone produced tachycardia slowing in the loading phase and early maintenance phase, the time to control the arrhythmia completely in the case of atrioventricular re-entrant tachycardia runs was up to 96 h. However, as all patients with effective or partially effective amiodarone therapy had improved already haemodynamically with rate slowing, no further concomitant anti-arrhythmic agents were used.

Drug side-effects

A marked QTc prolongation was seen in most patients with a median QTc of 428 ms (range 397–569 ms) after the intravenous drug loading dose compared to a median QTC of 476 ms (range 375–576 ms) at hospital discharge. However, as concomitant drugs and rhythm changes also influenced the repolarisation, no meaningful statistical analyses can be obtained about the significance of the QTc prolongation. QTc > 500 ms were only seen in infants with bundle branch block, intraventricular block and Wolff-Parkinson-White syndrome. Maintenance dosages of 12.5 and 15 μg/kg per min caused sinusbradycardia around 100 beats per minute in two infants, however, resolved after dose reduction. Mild hypotension was seen in one patient on a maintenance dosage of 10 μg/kg per min which also resolved after dose reduction. Markedly elevated liver enzymes were observed and considered as a side-effect in an infant after arterial switch operation. As a potential liver toxic agent, amiodarone therapy was stopped in this patient whose arrhythmia had been controlled. Choreatic movements in one infant who presented with cardiogenic shock resolved over time under ongoing oral amiodarone therapy. Thyroid toxicity with T4 or TSH values outside the reference range for age was not observed.

Follow-up

In 22 infants, long-term amiodarone therapy was established with a median oral amiodarone dosage of 9 mg/kg per day (range 5–15 mg/kg per day). Combination therapies with oral propafenone were instituted in two patients with partial intravenous amiodarone effect and in two patients who showed tachycardia breakthroughs on oral amiodarone. Oral amiodarone therapy was continued for a median period of 12 months (range 1–31 months). Arrhythmias resolved spontaneously in 17 infants or did not need further treatment in one infant. Thyroid dysfunction or elevated liver enzymes were not observed in infants on oral amiodarone treatment. During up to 72 months of follow-up, five infants died unrelated to amiodarone therapy, three with dilative cardiomyopathy due to pump failure, one due to other congenital malformations and one due to cerebral bleeding while on anticoagulant therapy.

Discussion

Arrhythmia control

Intravenous amiodarone was given to 23 newborns and infants with incessant, life-threatening supraventricular and ventricular tachycardias because of its high anti-arrhythmic efficacy combined with low negative inotropic effect [3, 4,7]. Although there was a large spectrum of

arrhythmias, six infants presented with ventricular tachycardias. More than 50% of the patients had congenital heart disease or cardiomyopathies and eight infants had undergone cardiac surgery. With a median age of 8 days, the majority of patients were very sick newborns who were haemodynamically unstable. Nevertheless, intravenous amiodarone was very effective and terminated the tachycardias in 19 of 23 infants. A partial effect in three infants allowed haemodynamic stabilisation. These success rates are comparable to other studies including older paediatric patients [1, 3, 4,6]. However, the high success rate in arrhythmia control despite pro-arrhythmogenic drug applications, electrolyte shifts and increased sympathetic drive due to post-operative stress in some patients, is remarkable. Noteworthy is also that intravenous amiodarone did not aggravate haemodynamic instability.

Amiodarone administration

Although amiodarone was given intravenously, it took a median time of 24 h to control the arrhythmia which may seem a long time in a life-threatening situation. Other groups also observed similar time periods until arrhythmia control [4]. However, as all patients had already improved haemodynamically in the intravenous drug loading or early maintenance phase by rate slowing of the tachycardia, a premature change in anti-arrhythmic management was avoided. Compared to published drug dosage recommendations, the median required intravenous maintenance dosage of 15 μg/kg per min is high. This may be a consequence of poor perfusion in haemodynamically compromised patients with slow tissue uptake and not a countereffect of inotropes as the required maintenance dosage was similar in patients with and without inotropic support. However, it appeared that the maximum effective intravenous maintenance dosage is in the range of 20–25 μg/kg per min. As in other reports, the median time of 5 days intravenous amiodarone demonstrates also the major effort required to stabilise the patients haemodynamically and to guarantee absorption of the drug when intravenous amiodarone is replaced by oral amiodarone [4].

Safety of amiodarone

Intravenous amiodarone proved to be a safe therapy in infants. Like in other studies, no severe pro-arrhythmic effects were seen [3]. Sinus bradycardia could be easily resolved by dosage reduction. QTc prolongations >500 ms were only seen in patients with abnormal depolarisation such as Wolff-Parkinson-White syndrome and intraventricular or bundle branch block. Systemic side-effects like hypotension in one patient could be adequately recognised and resolved by dose reduction. Thus, there was little indication of a marked negative inotropic effect of intravenous amiodarone. Compared to reports concerning hypotension following bolus administration of intravenous amiodarone in adults, the rarity of hypotensive side-effects in our patients demonstrates the haemodynamically better tolerance of loading and maintenance infusions. However, newer aqueous intravenous amiodarone solutions lacking hypotensive solvents may minimise the risk of hypotension even further [5,11]. Despite the mild pro-arrhythmic and haemodynamic side-effects, a close cardiovascular monitoring in an intensive care setting of all patients receiving intravenous amiodarone is strongly recommended. Elevated liver enzymes in one patient after cardiac surgery was possibly due to a combination of liver toxic effects. Amiodarone cessation may be warranted in such patients in order to avoid further liver damage. Choreatic movements in one patient resolved over time. Although a transient neurological complication occurred in only a single infant other studies indicate that neurological side-effects of amiodarone and other anti-arrhythmic drugs are far more common [2]. Further follow-up in 22 infants after replacement with oral amiodarone did not reveal significant pro-arrhythmic effects, elevated liver enzymes or thyroid dysfunction. Due to the age of the patient group, photosensitivity with skin discolouration was not an issue. As amiodarone therapy was only meant to be a temporary anti-arrhythmic therapy up to about a year, long-term side-effects such as cornea deposits or pulmonary fibroses were not expected [3].

In this study with a small number of patients, intravenous amiodarone was a safe and effective therapy for life-threatening incessant tachycardias in infants. However, taking the various potential side-effects into consideration, intravenous amiodarone therapy should still be reserved for those infants with incessant tachycardias and severe haemodynamic compromise in whom D/C cardioversion, overdrive pacing or intravenous adenosine is not successful or not applicable. Further studies are needed before definitive recommendations can be made about the administration of amiodarone in infants.

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